Visual activation of auditory cortex reflects maladaptive plasticity in cochlear implant users

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Visual activation of auditory cortex reflects maladaptive plasticity in cochlear implant users

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Cross-modal reorganization in the auditory cortex has been reported in deaf individuals. However, it is not well understood whether this compensatory reorganization induced by auditory deprivation recedes once the sensation of hearing is partially restored through a cochlear implant. The current study used electroencephalography source localization to examine cross-modal reorganization in the auditory cortex of post-lingually deafened cochlear implant users. We analysed visual-evoked potentials to parametrically modulated reversing chequerboard images between cochlear implant users ($n = 11$) and normal-hearing listeners ($n = 11$). The results revealed smaller P100 amplitudes and reduced visual cortex activation in cochlear implant users compared with normal-hearing listeners. At the P100 latency, cochlear implant users also showed activation in the right auditory cortex, which was inversely related to speech recognition ability with the cochlear implant. These results confirm a visual take-over in the auditory cortex of cochlear implant users. Incomplete reversal of this deafness-induced cortical reorganization might limit clinical benefit from a cochlear implant and help explain the high inter-subject variability in auditory speech comprehension.

Keywords: cochlear implant; rehabilitation; auditory cortex; visual-evoked potential; cross-modal plasticity
Abbreviation: sLORETA = standardized low-resolution brain electromagnetic tomography; VEP = visual-evoked potential

Introduction

Cochlear implants can restore hearing in individuals suffering from profound hearing loss. This bionic device transforms the acoustic signal into current pulses and directly stimulates the residual fibres of the auditory nerve. Following implantation, cochlear implant users show cortical changes in the auditory system as they adapt to the new input provided by the cochlear implant (Giraud *et al.*, 2001*b*; Pantev *et al.*, 2006). In particular, longer cochlear implant experience has been related to enhanced recruitment of the auditory cortex (Pantev *et al.*, 2006; Sandmann *et al.*, 2009) and higher functional specialization of the auditory system

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(Giraud et al., 2001b). This reorganization in the auditory cortex following implantation may be based on alteration in Ca^{2+}-dependent signalling events (Tan et al., 2008), and seems to be located both in the contra- and the ipsilateral hemisphere to the cochlear implant device (Kral et al., 2002; Sandmann et al., 2009). Thus, alteration of auditory experience through electrical input after cochlear implantation leads to functional changes in the auditory system. Recently, it has been recognized that the capacity for cortical plasticity seems at least as important as technical development for cochlear implant success (Moore and Shannon, 2009).

Functional changes induced by auditory experience are not limited to the auditory cortex, but can also extend across different sensory systems (Bavelier and Neville, 2002; Merabet and Pascual-Leone, 2010). Individuals deprived of auditory input can compensate with superior specific abilities in the remaining sensory modalities, including (but not limited to) improved motion processing in the peripheral visual field (Bavelier et al., 2006; Mitchell and Maslin, 2007) and enhanced tactile sensitivity (Levanen and Hamdorf, 2001). The neural substrate for these behavioural improvements may reside in the deprived auditory cortex that is reorganized by the spared sensory modalities (Bavelier and Neville, 2002; Merabet and Pascual-Leone, 2010). Accordingly, cross-modal reorganization of the auditory cortex has been observed in profoundly deaf individuals, showing responses to visual (Finney et al., 2001, 2003; Fine et al., 2005) and vibrotactile stimuli in the auditory cortex (Levanen et al., 1998; Auer et al., 2007). These cross-modal changes associated with auditory deprivation appear to be localized to specific auditory cortical subregions and may follow organizational principles that maintain the functional specialization of the recruited brain regions (Lomber et al., 2010; Dormal and Collignon, 2011; Meredith et al., 2011).

Cortical reorganization in deaf individuals might have beneficial effects during the period of deafness (Bavelier et al., 2006; Mitchell and Maslin, 2007), but could have detrimental consequences for the adaptation to the new, electrical input after cochlear implantation (Merabet and Pascual-Leone, 2010). In particular, cross-modal changes of the deaf auditory cortex might hinder its recruitment by the cochlear implant input if this cortical structure has been functionally reorganized by the spared sensory modalities. This line of reasoning is supported by the observation that prelingually deafened individuals with pronounced cross-modal take-over of auditory regions are less likely to benefit from implantation (Lee et al., 2001, 2007; Giraud and Lee, 2007). Furthermore, indirect evidence in support of this hypothesis comes from two EEG studies, which suggest that poor speech perception ability with a cochlear implant is related to enhanced amplitudes of visual-evoked brain activity over anterior and temporal scalp regions, at least in prelingually deafened cochlear implant users (Doucet et al., 2006; Buckley and Tobey, 2011). Thus, despite the restored input, poor cochlear implant performers may continue to recruit additional regions in the auditory cortex for visual processing.

Understanding functional changes in cochlear implant users could be of substantial clinical value because it may help predict and evaluate the success of cochlear implantation. Accordingly, it has been suggested that limited auditory benefit from a cochlear implant is related to visual-to-auditory cross-modal reorganization in the auditory cortex (Lee et al., 2001; Doucet et al., 2006). To test this hypothesis, we used parametrically modulated reversing chequerboard images to examine how the physical property of luminance affects early visual-evoked potentials (VEPs), that is, initial stages of visual processing that are strongly influenced by physical stimulus properties. Previous results have shown larger VEP responses for higher luminance levels in the visual stimuli (Armington, 1968; Johannes et al., 1995), leading to our prediction of a parametric modulation of early VEP components as a function of overall luminance in the chequerboard images. Moreover, we expected a functional difference between cochlear implant users and normal-hearing listeners already at early processing levels in the visual hierarchy, given the previous finding that auditory deprivation can affect early VEP amplitudes, at least in congenitally deaf individuals (Neville and Lawson, 1987; Armstrong et al., 2002). To examine cross-modal reorganization in the auditory cortex of cochlear implant users, we applied EEG standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002), which allowed the analysis of auditory cortex activity in response to visual stimulation. While EEG source localization suffers from the inverse problem, alternative neuroimaging techniques appear even less feasible. PET and functional MRI have poor temporal resolution and functional MRI in particular is potentially invasive for cochlear implant users (Giraud et al., 2001b; Seghier et al., 2005; Majdani et al., 2008). Moreover, whole-head magnetoencephalography suffers from strong electromagnetic interference induced by the cochlear implant device (Pantev et al., 2006), further reducing options for the study of auditory cortex activity to EEG.

Materials and methods

Participants

Twenty-four adult volunteers (12 females, 12 males) participated in the study. All participants were consistent right-handers (Annett, 1970) and had normal or corrected-to-normal vision. None of the participants had a history of psychiatric illness. Twelve of the participants were post-lingually deafened cochlear implant users. One of the cochlear implant users was excluded from further analysis due to outliers in EEG measurements (exclusion criterion: VEP measures exceeding 2 SDs from the mean). Among the remaining 11 cochlear implant users, four individuals were implanted bilaterally and seven were implanted unilaterally (Table 1). Five of the unilaterally implanted cochlear implant users were implanted in the right ear and two in the left ear. All cochlear implant users used a Nucleus cochlear implant system with a Freedom processor (Patrick et al., 2006), and they had been using their cochlear implant continuously for at least 12 months before the experiment (mean and standard error: 76 ± 18 months; range: 12–240 months). None of the cochlear implant users used sign language to communicate. It is often difficult to estimate the exact point in time of 'onset of profound deafness' and to derive from that an estimate for the 'duration of deafness', in particular in individuals with progressive hearing loss. Therefore, we have used a pragmatic definition of this clinical parameter. The 'age at onset of profound deafness' refers to the age at which the amount of hearing loss was found to be too severe to be successfully treated with a conventional hearing aid.

Table 1 Subject demographics of cochlear implant users

Subject	Gender	Age	Implanted ear	Aetiology	Age at onset of profound deafness (years)	Duration of deafness (years)	Cochlear implant use left side (months)	Cochlear implant use right side (months)	Freiburg monosyllabic word test (%)	Oldenburg sentences test (dB)
1	Male	56	Right	Progressive	52	1	–	46	100	2.1
2	Female	60	Left and right	Congenital	51	1	79	85	Left: 70 right: 75	Left: −9 right: −6.7
3	Female	52	Left and right	Progressive	36	15	195	14	Left: 85 right: 100	Left: 0.8 right: −4.7
4	Female	47	Left	Progressive	42	2	50	–	75	Not measurable
5	Female	55	Left and right	Congenital	42	7	40	156	Left: 100 right: 75	Left: −4.5 right: −2.5
6	Male	69	Left	Progressive	55	2	102	–	80	−0.2
7	Male	65	Left and right	Sudden deafness	31	13	240	38	Left: 60 right: 75	Left: 5 right: 6
8	Male	52	Right	Progressive	44	1	–	54	85	−10.5
9	Male	42	Right	Meningitis	37	4	–	12	75	−4.3
10	Female	38	Right	Progressive	37	1	–	12	100	−8
11	Female	58	Right	Progressive	56	1	–	18	90	−7

Speech recognition without lip-reading (e.g. telephone) at this point was insufficient. The 'duration of deafness' is defined as the time between the 'age at onset of profound deafness' and the date of cochlear implant surgery. Because of the considerable age variance across the implanted individuals (mean and standard error: 54 ± 3 years; range 38–69 years), each cochlear implant user was matched with a normal-hearing listener for gender and age (mean and standard error: 56 ± 3 years; range 38–70 years). The normal-hearing listeners served as controls and had normal hearing, as defined by <20 dB hearing loss in the tested ear (500–4000 Hz). To keep the control group and the cochlear implant group equal, the exclusion of a cochlear implant user (as described above) led to the exclusion of his match from the normal-hearing control group. All participants gave written informed consent prior to the experiment. The study was carried out in accordance with the Declaration of Helsinki principles and was approved by the ethics committee of the University of Zurich.

Stimuli

The stimuli consisted of reversing displays of chequerboard patterns, based on a monochrome image pair (Fig. 1). The image pair of each stimulus is referred to as Images A and B. Image B was generated by rotating Image A through 180°. All stimuli (1280×1024 pixels) had a radial nature and consisted of 20 rings, each of which was divided into 18 sectors with neighbouring sectors being of opposite phase. The radial nature of the stimuli compensated for the increase in receptive-field size with eccentricity (Zemon and Ratliff, 1982; Rover and Bach, 1985). The luminance for white pixels was 138.6 cd/m^2 and for black pixels 0.25 cd/m^2 (Minolta: LS 110), representing a Michelson contrast of 99.6%. Images A and B changed at a reversal rate of 2 Hz. There were four different pairs of chequerboard patterns, which systematically varied in terms of luminance ratio. The proportion of white pixels in the stimulus pattern was set at 1/8 (Level 1: corresponds to 12.5% white pixels), 2/8 (Level 2: corresponds to 25% white pixels), 3/8 (Level 3: corresponds to 37.5% white pixels) and 4/8 (Level 4: corresponds to 50% white pixels). The contrast between white and black pixels was identical in all images used.

Although previous studies concerning visual processing in deaf individuals and cochlear implant users have focused on motion stimuli (Bavelier *et al.*, 2000, 2001; Finney *et al.*, 2001; Armstrong *et al.*, 2002; Fine *et al.*, 2005; Buckley and Tobey, 2011), the present study used parametric modulations of reversing chequerboard images for the following reasons. First, motion stimuli evoke motion-specific VEP signatures from ~150 to 200 ms (Armstrong *et al.*, 2002), whereas chequerboard reversals elicit strong, high signal-to-noise ratio VEPs even at shorter latencies, likely reflecting an earlier or more basic, low-level step of exogenous visual processing. Thus, the use of reversing chequerboard stimuli allowed the examination of early stages of visual information processing. Second, pattern reversal stimuli consisting of black and white checks are used in the clinical context because pattern-reversal VEPs can provide important diagnostic information regarding the functional integrity of the visual system (Odom *et al.*, 2010). Third, VEPs elicited by reversing chequerboard patterns are less variable in waveform morphology and latency than responses to other types of visual stimulation, such as pattern onset/offset response (Odom *et al.*, 2004). Fourth, chequerboards can be easily parametrically modulated, which was important in our study to evaluate whether this parametric manipulation would be reflected in auditory cortex activity, indicating functional, i.e. visual processing, relevance. Finally, the aim of the present study was to measure VEPs with a good signal-to-noise ratio, that is, VEPs with good quality, within a reasonable recording time. Using the conservative plus–minus approach

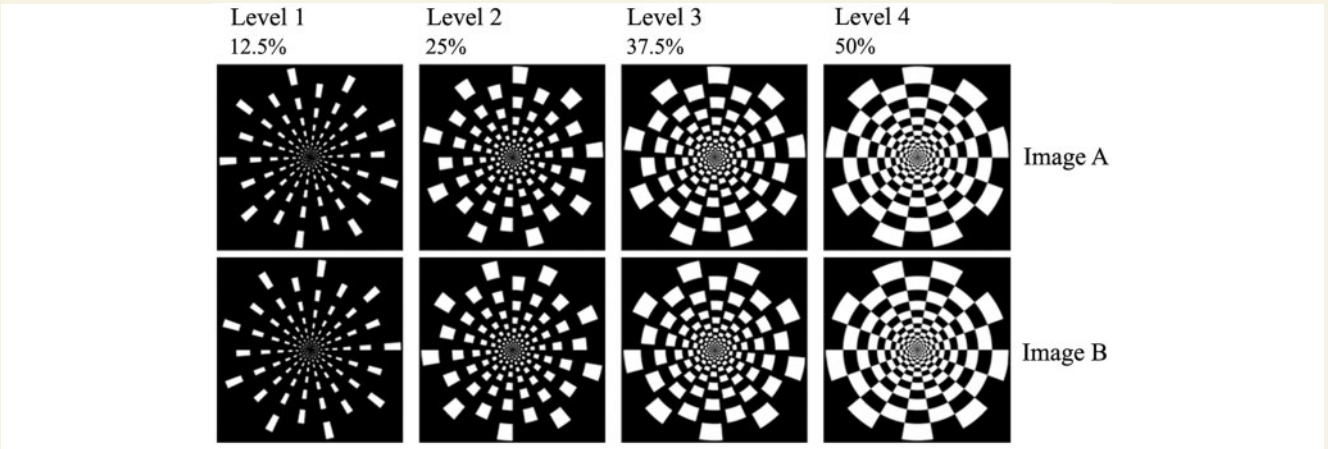

Figure 1 The pattern reversal stimuli. Four different chequerboard patterns with parametrically modulated luminance ratios were presented in separate experimental blocks. The proportion of white pixels in the stimulus patterns was 12.5% (Level 1), 25% (Level 2), 37.5% (Level 3) and 50% (Level 4). Note that the two images (Images A and B) in each level were identical; with Image B being generated by rotating Image A through 180°.

(Schimmel *et al.*, 1967; Viola *et al.*, 2011), we estimated the signal and noise in our VEPs at the same latency range after stimulus onset (50–122 ms), scaled to decibel [20log10(signal/noise)]. This analysis revealed a high signal-to-noise ratio in the P100 VEPs of all conditions (mean and standard errors of the mean: Level 1: 17.7 ± 1.2 dB; Level 2: 18.3 ± 1.9 dB; Level 3: 20.4 ± 1.8 dB; and Level 4: 23.6 ± 1.5 dB), which is particularly important for adequate EEG source localization. Moreover, a high signal-to-noise ratio in VEPs is relevant in the clinical context, as it helps to avoid impaired vigilance, motivational and other problems associated with intolerably long recording times.

Procedure

Participants were seated in front of a computer screen in a darkened and electromagnetically shielded room. The stimuli were presented on a 19-inch computer monitor (Belinea BT10002) at a viewing distance of 90 cm. The stimuli occupied a visual angle of 15°. Participants performed four experimental blocks (i.e. conditions) in which they were presented with one of the four image pairs. The block order was counterbalanced across participants. In the course of the experimental session, each chequerboard image was repeated 60 times, resulting in a total of 480 stimuli (four conditions × two images × 60 repetitions). Stimulus duration and interstimulus interval between successive images were 500 ms. Participants were carefully instructed before each condition to fixate the centre of the chequerboard images. After each experimental block, participants rested for ∼1 min.

Electroencephalography recording

EEG was continuously recorded by 60 Ag/AgCl electrodes placed according to the 10–10 system. Three additional electrodes were placed on the outer canthi of both eyes and below the left eye to record electro-oculograms. Using two BrainAmp amplifiers (Brainproducts, http://www.brainproducts.de), all channels were recorded against a nose-tip reference. EEG and electro-oculograms were filtered from 0.02 to 250 Hz and recorded with a sampling rate of 1000 Hz. Electrode impedances were kept below 10 kΩ.

Electroencephalography data processing

EEG data were analysed using EEGLAB (Delorme and Makeig, 2004) running in the MATLAB environment (Mathworks). Imported data were offline bandpass filtered (1–45 Hz) and down-sampled to 500 Hz (Debener *et al.*, 2010). In cochlear implant users, missing channels located over the region of the speech processor and transmitter coil were interpolated (mean and standard error: 3 ± 0.5 electrodes; range: 1–7 electrodes), a procedure that still allows good dipole source localization of auditory-evoked potentials in cochlear implant users (Debener *et al.*, 2008; Sandmann *et al.*, 2009). EEG was re-referenced to a common average reference and segmented into epochs from −62 to 448 ms relative to stimulus onset. After baseline correction (−62 to 0 ms), artefacts were rejected using an amplitude threshold criterion of ±200 μV. Independent component analysis was then applied to the segmented data to identify and attenuate ocular artefacts and other sources of non-cerebral activity (Jung *et al.*, 2000*a*, *b*). After artefact correction, single trials from all electrodes were further denoised using an algorithm based on the wavelet transform (Quian Quiroga and Garcia, 2003), as done previously (Sandmann *et al.*, 2009, 2010; Geiser *et al.*, 2010). Subsequent peak analysis of VEPs was performed on single-subject averages measured at channel Oz, which showed the largest deflections in the grand average. For VEP quantification, individual amplitudes and latencies were measured by detecting the most positive (P270) or negative (N150) deflection relative to baseline. Following recommendations, the P100 VEP was quantified by measuring the peak-to-peak amplitude of the P100 relative to the preceding N75 peak (Odom *et al.*, 2010). P100 peak latencies were measured from the most positive peak occurring at 82–122 ms after stimulus onset. In general, latency ranges for VEP amplitude detection (N75–P100: 50–122 ms; N150: 124–204 ms; P270: 230–330 ms) were defined on the basis of the grand average computed across all conditions and participants.

Amplitudes and latencies of VEPs (P100, N150 and P270) were analysed using separate repeated-measures ANOVAs, with condition (Levels 1–4) as within-subjects factor and group (cochlear implant users and normal-hearing listeners) as between-subjects factor. Significant main effects and interactions ($P < 0.05$) were followed-up

with *post hoc* *t*-tests, and the Greenhouse–Geisser correction was applied to compensate for violations of the sphericity assumption. Subsequently, a linear regression analysis was conducted on amplitudes and latencies of each VEP component to assess VEP modulations across the four conditions. Regression coefficients obtained from this analysis were subjected to one-sample, two-tailed *t*-tests in order to test for significant linear VEP modulations. Finally, regression coefficients for each VEP component were subjected to independent samples *t*-tests to compare VEP modulations between cochlear implant users and normal-hearing listeners.

Single-trial analysis of P100 latency variability

Because cochlear implant users and normal-hearing listeners showed systematic differences for the P100 amplitude, we analysed the variability of single-trial P100 latency for each participant. This allowed the hypothesis that smaller P100 amplitudes in cochlear implant users originate from higher single-trial variability in cochlear implant users compared with normal-hearing listeners, to be tested. In a first step, we analysed the single-trial P100 latency jitter for each participant by computing the cross-correlation between a template (grand average at Oz electrode: 84–124 ms) and each single-trial epoch at the Oz electrode (Woody, 1967; Spencer, 2005). Latency variability of single trials was estimated from the time lag at which the cross-correlation value was a maximum. In a second step, we assessed the effect of latency jitter correction on the P100 VEP in order to examine whether the correction for single-trial latency jitter would cancel out the VEP difference between cochlear implant users and normal-hearing listeners. This correction of latency jitter was done by shifting every single trial of each participant in time according to the time lags (between the template and the single trials) as estimated in the first step. Afterwards, P100 amplitudes of latency-corrected VEPs were measured from the preceding N75 peak (Odom *et al.*, 2010). The effect of latency jitter correction was assessed by computing a P100 peak correction index [(peak after–peak before)/peak after + peak before) × 100] for each participant. Finally, the peak correction index and P100 peak measures (before and after latency jitter correction) were compared between cochlear implant users and normal-hearing listeners by means of independent samples *t*-tests.

Standardized low-resolution brain electromagnetic tomography

Scalp-recorded VEP amplitudes were evaluated by sLORETA, which allowed the analysis of the location of active sources for visual processing in cochlear implant users and normal-hearing listeners (Pascual-Marqui, 2002). The sLORETA method computes the cortical distribution of neuronal electrical activity from scalp-recorded electric potentials, thus not requiring assumptions on the number of putatively existing dipoles. This method has the property of exact localization (Sekihara *et al.*, 2005), albeit with low spatial resolution. More specifically, exact localization means that when the tomography is tested with point sources anywhere in the brain, it produces blurred images with the maximum activation located exactly at the actual location. Since this is distributed linear tomography, it is then guaranteed that any distribution of activity will be properly localized in a blurred (i.e. low spatial resolution) way. If two simultaneously active sources are closer than 1.5 cm, then they are not resolved, i.e. they are observed as a single blurred focus, with maximum activity between the two sources. Recent experimental validation for sLORETA has been provided by Plummer and colleagues (2010), based on ground truth obtained from intracranial recordings in epilepsy patients and showing that sLORETA provided the lowest localization error.

Similar to the analysis of single-trial latency jitter, the sLORETA analysis focused on the P100 VEP since scalp-recorded potentials revealed systematic differences between cochlear implant users and normal-hearing listeners specifically at the P100 latency. Source estimates were baseline-corrected (−62 to 0 ms), scaled for the global mean for each timeframe and averaged over the time interval corresponding to the scalp-recorded P100 (98–118 ms). Afterwards, sLORETA source estimates were subjected to an independent samples *t*-test in order to compare active sources between cochlear implant users and normal-hearing listeners. A region of interest analysis was then applied to systematically analyse the modulation of cortical activation across the four conditions. An anatomical region of interest was defined in the visual [Brodmann area (BA) 18] and in the auditory cortex (BA41 and 42) of each hemisphere, respectively. The definition of the two regions of interest was based on previous literature, suggesting that the pattern-reversal P100 VEP is generated in the secondary visual cortex (Notachtar *et al.*, 1993; Onofrj *et al.*, 1995*a*, *b*), and showing that the primary and secondary auditory cortex is activated for visual processing in deaf individuals (Finney *et al.*, 2001; Fine *et al.*, 2005). For statistical analysis, current density values of each region of interest (visual and auditory) were subjected to separate repeated-measures ANOVAs, with condition (Levels 1–4) and hemisphere (left and right) as within-subjects factors and group (cochlear implant users, normal-hearing listeners) as between-subjects factor. Significant main effects and interactions ($P < 0.05$) were followed-up with *post hoc* *t*-tests, and the Greenhouse–Geisser correction was applied in case of violation of the sphericity assumption. Similar to the procedures used for the analysis of scalp-recorded VEPs, current densities of each region of interest were subjected to a linear regression analysis and subsequent *t*-tests on the regression coefficients were applied to test for linear modulations of cortical activation across the four conditions in cochlear implant users and normal-hearing listeners.

In order to specifically examine visual-induced activation in the auditory cortex at P100 latency (98–118 ms), current densities of the left and right auditory region of interest were subjected to one-sample *t*-tests. Moreover, the time course of visual-induced activation in the visual and auditory cortex was analysed by using a non-parametric bootstrapping procedure that tested for significant differences between cochlear implant users and normal-hearing listeners (Efron and Tibshirani, 1994). Confidence limits of 99.9% were obtained for difference waves based on 2000 iterations. Similar to previous studies, source waveforms were considered significantly different if the confidence interval of the difference wave did not include zero (Hine and Debener, 2008; Sandmann *et al.*, 2009).

Results

Visual-evoked potentials

Cochlear implant users and normal-hearing listeners revealed VEPs with maximal deflections at occipital channels (Fig. 2). For both groups, the grand averages showed four distinct peaks around 76 ms (referred to as N75), 108 ms (referred to as P100), 152 ms (referred to as N150) and 268 ms (referred to as P270) after visual stimulus onset. Statistical comparison of evoked potentials (P100, N150, P270) to Images A and B of each image pair

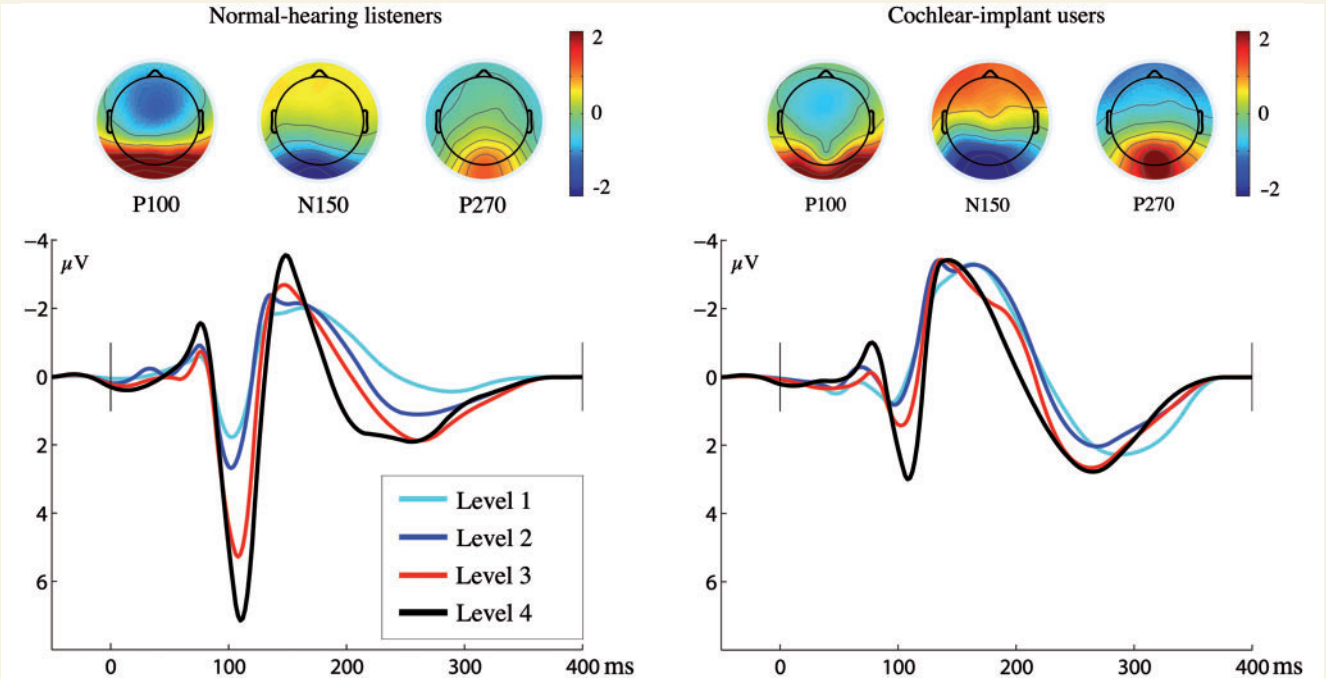

Figure 2 Scalp-recorded VEPs. Topographies of grand average VEPs computed across all luminance ratios (*top*). The topographies show the P100 (108 ms), N150 (152 ms) and P270 VEPs (268 ms) and are given separately for normal-hearing listeners and cochlear implant users. Grand average VEPs recorded at channel Oz are shown for different luminance ratios (Levels 1–4) (*bottom*). Level 1 refers to the smallest proportion (12.5%), Level 4 to the largest proportion (50%) of white pixels in the stimulus pattern.

(Levels 1–4) revealed no significant difference (amplitudes: $P > 0.07$; latencies: $P > 0.1$), except for P100 latency at Level 4 ($P < 0.01$). Thus, VEPs of each image pair were collapsed for further statistical analyses.

Figure 3 shows VEP amplitudes and latencies for different luminance ratios separately for cochlear implant users and normal-hearing listeners. Repeated-measures ANOVAs on P100 amplitudes revealed significant main effects for condition [$F(1.6,31.3) = 28.2$, $P < 0.001$] and group [$F(1,20) = 6.4$, $P < 0.05$], and a significant interaction between condition and group [$F(3,60) = 6.0$, $P = 0.01$]. Similarly, a main effect for condition [$F(3,60) = 15.1$, $P < 0.001$] and group [$F(1,20) = 4.9$, $P < 0.05$] was found for P100 latencies. Furthermore, we found a significant main effect for conditions for both the P270 amplitudes [$F(2,40.8) = 6.0$, $P < 0.01$] and the P270 latencies [$F(2.3,46.1) = 8.8$, $P < 0.001$]. Independent sample *t*-tests on VEP amplitudes in separate conditions showed smaller P100 amplitudes in cochlear implant users than normal-hearing listeners ($P < 0.05$), specifically for stimulus patterns with higher proportion of white pixels (Levels 2–4). Cochlear implant users also revealed shorter P100 latencies for Level 1 when compared to normal-hearing listeners ($P < 0.01$).

The mean regression coefficients for VEP amplitudes and latencies are provided in Table 2. Zero-mean *t*-tests on regression coefficients revealed a significant effect of luminance ratio on P100 VEPs in cochlear implant users (amplitude, $P < 0.05$; latency, $P < 0.01$) and normal-hearing listeners (amplitude, $P < 0.001$; latency, $P < 0.01$). A significant effect of luminance ratio was also found in both groups for the P270 amplitudes (cochlear implant users, normal-hearing listeners: $P < 0.05$), and in cochlear implant users for P270 latencies ($P < 0.01$). The comparison of regression coefficients between the two groups of participants revealed that normal-hearing listeners had stronger modulation of P100 amplitudes across the four luminance levels ($P < 0.05$).

Single-trial analysis of P100 latency variability

The single-trial analysis of P100 latency jitter was performed in order to examine whether higher single-trial variability in cochlear implant users accounts for overall smaller P100 amplitudes in cochlear implant users compared with normal-hearing listeners. The results of this analysis revealed a trend for higher single-trial variability of P100 latency in cochlear implant users than normal-hearing listeners ($P = 0.08$). In a second step, we examined how the correction of single-trial latency jitter affects the P100 amplitude. The correction of single-trial latency jitter led to enhanced P100 amplitudes in both the cochlear implant users and normal-hearing listeners (Supplementary Fig. 1A). However, the P100 peak correction index [(peak after–peak before)/(peak after + peak before) × 100] was not significantly different between cochlear implant users and normal-hearing listeners ($P = 0.12$), indicating similar increase in P100 amplitude for the two groups due to latency jitter correction. Moreover, P100 amplitudes were smaller in cochlear implant users compared with

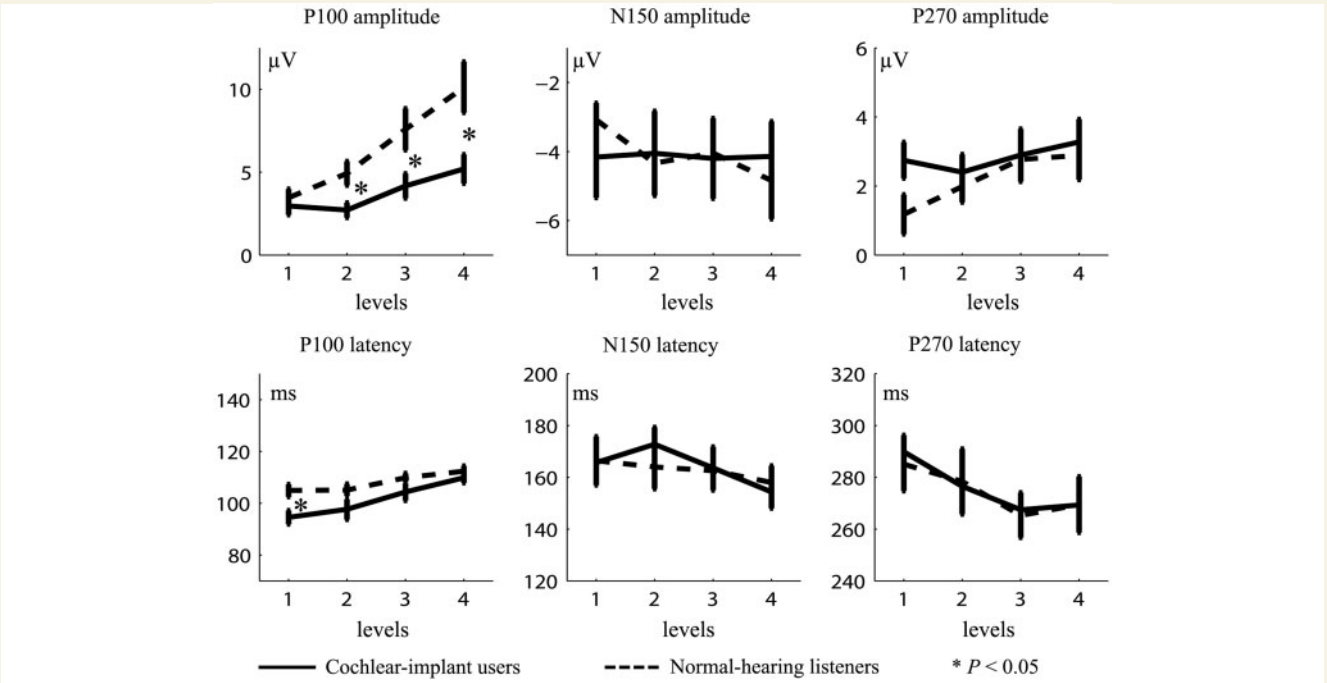

Figure 3 Modulation of scalp-recorded VEPs across different luminance ratios. The figure shows amplitudes and latencies of the P100, N150 and P270 VEPs separately for cochlear implant users (solid line) and normal-hearing listeners (dashed line). Level 1 refers to the smallest proportion (12.5%), Level 4 to the largest proportion (50%) of white pixels in the stimulus pattern. The asterisk indicates significantly different VEP amplitudes between cochlear implant users and normal-hearing listeners ($P < 0.05$). Note the different scaling for different VEP components.

Table 2 Regression coefficients for VEP measures (amplitudes, latencies) and current source densities

Group	P100		N150		P270		Visual region of interest		Auditory region of interest	
	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Left	Right	Left	Right
Cochlear implant users	2.5 ± 0.9	15.8 ± 3.6	0 ± 0.9	−12.9 ± 8.0	0.6 ± 0.3	−21.2 ± 5.6	2.9 ± 1	1.6 ± 1.4	0.3 ± 0.1	0.9 ± 0.5
Normal-hearing listeners	6.8 ± 1.3	8.1 ± 2.5	−1.4 ± 0.9	−8.0 ± 7.5	1.8 ± 0.7	−18 ± 8.8	8.3 ± 2.6	9.7 ± 4.8	0.1 ± 0.2	0.1 ± 0.1

normal-hearing listeners before, as well as after latency jitter correction ($P < 0.05$; Supplementary Fig. 1B). In sum, these results suggest that cochlear implant users tend to show higher variability in single trials of VEPs. However, this trend for higher variability from trial to trial in cochlear implant users cannot account for the finding of overall smaller P100 amplitudes in cochlear implant users compared with normal-hearing listeners. The results of this analysis strongly suggest a different degree of visual cortex recruitment between cochlear implant users and normal-hearing listeners.

sLORETA source estimations

Source estimation of the grand average P100 VEP (computed across all participants and conditions) revealed maximal activation over BA18 and BA19 in the left and right hemisphere. Independent samples *t*-tests of individual P100 source estimates showed that activation in these cortical regions was significantly reduced in cochlear implant users compared with normal-hearing listeners (Fig. 4A). In particular, cochlear implant users revealed bilaterally reduced activation over BA18, extending to BA17 in both hemispheres and BA19 in the left hemisphere ($P < 0.01$).

The region of interest analysis confirmed differences in cortical activation between cochlear implant users and normal-hearing listeners at P100 latency (Fig. 4B). Repeated-measures ANOVAs on the visual region of interest revealed significant main effects of condition [$F(1.2,23.8) = 8.9$, $P < 0.01$] and group [$F(1,20) = 5.5$, $P < 0.05$]. Similarly, a significant main effect for group was found for the auditory region of interest [$F(1,20) = 4.7$, $P < 0.05$]. *Post hoc* *t*-tests revealed larger activation in the left visual region of interest (all levels: $P < 0.05$), and a trend for significantly larger activation in the right visual region of interest (Level 4:

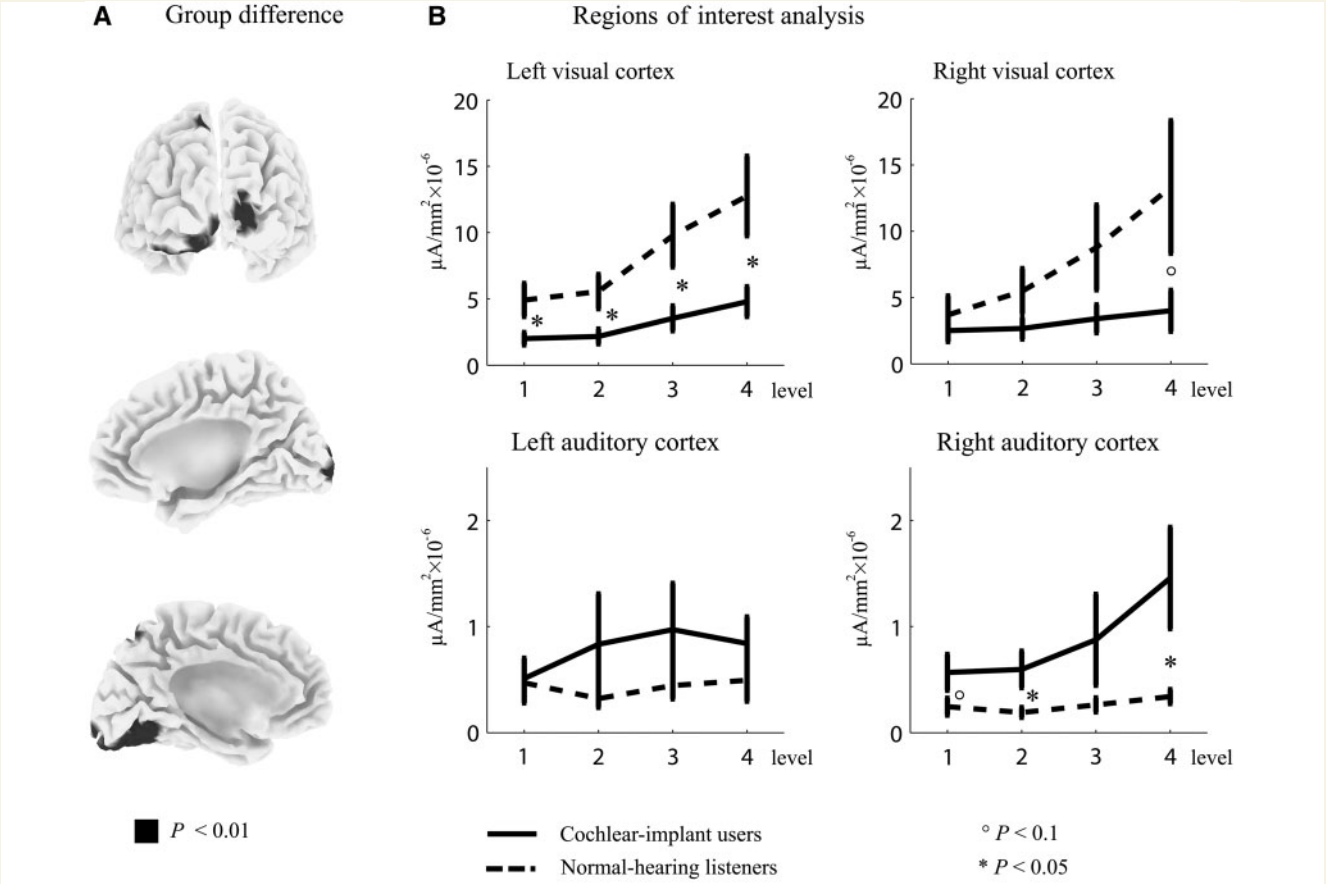

Figure 4 Source analysis of the P100 VEP. (**A**) Comparison of sLORETA source estimates between cochlear implant users and normal-hearing listeners. Cochlear implant users showed reduced activation in the visual cortex than normal-hearing listeners, with the strongest group difference located over the secondary visual cortex in the left and right hemisphere (BA 18). Significant differences between the two groups are coloured in black ($P < 0.001$). (**B**) Results from the regions of interest analysis. Plots illustrate cortical activation in the visual (BA 18) and auditory cortex (BA 41 and BA 42) of the left and right hemisphere. Note the interaction between activation in the auditory and visual cortex of normal-hearing listeners (dashed line) and cochlear implant users (solid line). Level 1 refers to the smallest proportion (12.5%), Level 4 to the largest proportion (50%) of white pixels in the stimulus pattern. The asterisk indicates a significant difference of cortical activation between normal-hearing listeners and cochlear implant users ($P < 0.05$). Note the different scaling for the visual and auditory regions of interest.

$P = 0.09$) for normal-hearing listeners than cochlear implant users. Conversely, results from the auditory region of interest showed enhanced activation in the right auditory cortex for cochlear implant users when compared with normal-hearing listeners (Level 1: $P = 0.1$; Level 2 and Level 4: $P < 0.05$).

The time course of activation in the visual and auditory regions of interest confirmed the expected between-group difference at early stages of visual processing in both the visual and auditory cortex (Supplementary Fig. 2). Moreover, the time course of activation also confirmed the generally smaller activation in the auditory cortex than in the visual cortex. Nevertheless, the results from one-sample *t*-tests at P100 latency (98–118 ms) showed that this visual-induced activation in the auditory cortex was significant (Supplementary Table 1) and was of functional relevance, as the parametric modulation was (at least partly) preserved in the auditory cortex of cochlear implant users (Fig. 4B).

The mean regression coefficients for current densities of each region of interest are provided in Table 2. As predicted by the effect of luminance ratio on scalp-recorded P100 amplitudes, the regression analysis showed that cortical activation in the visual region of interest was significantly modulated by luminance ratio in both the normal-hearing listeners (left visual cortex: $P < 0.05$; right visual cortex: $P = 0.07$) and the cochlear implant users (left visual cortex: $P < 0.05$). This modulation of visual cortex activation appeared to be stronger in normal-hearing listeners than in cochlear implant users, although significant thresholds were not met with a mean difference of 5.4 (left visual cortex) and 8.1 (right visual cortex) between regression coefficients of the two groups (left visual cortex: $P = 0.08$; right visual cortex: $P = 0.13$). Moreover, analysis of regression coefficients revealed an effect of luminance ratio on auditory cortex activation in cochlear implant users (left: $P < 0.05$; right: $P = 0.1$) but not in normal-hearing listeners (left, right: $P > 0.23$).

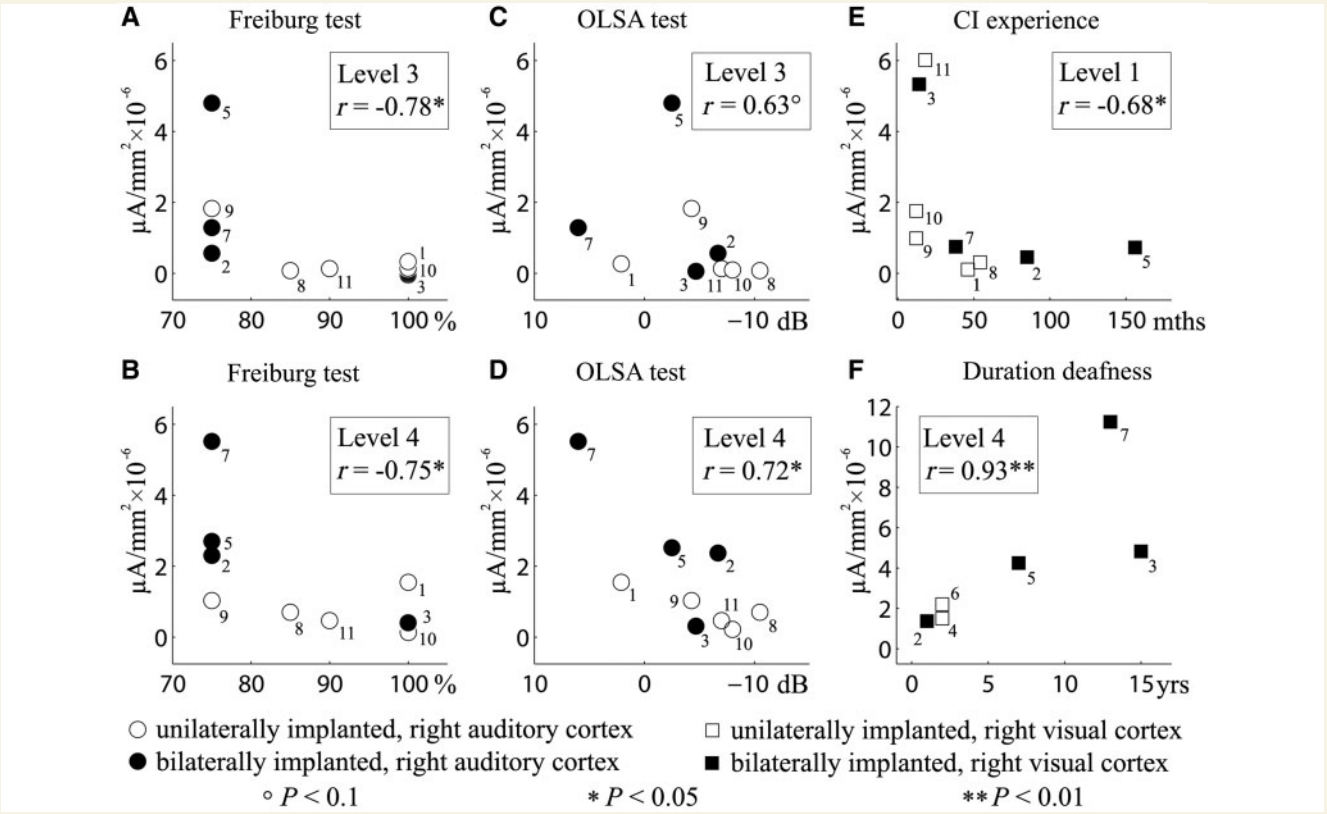

Figure 5 Significant non-parametric correlations between clinical parameters and activation in the visual and auditory cortex of cochlear implant users. (**A–D**) Relationship between activation in the right auditory cortex and speech intelligibility in individuals with a right ear implant. Speech intelligibility was measured by the Freiburg monosyllabic word test (**A** and **B**) and the Oldenburg sentences (OLSA) test (**C** and **D**). Note that in the Oldenburg sentences test, more negative decibel values indicate better perceptual performance. (**E**) Negative correlation between activation in the right visual cortex and duration of cochlear implant use in right-ear implanted individuals. (**F**) Positive correlation between activation in the right visual cortex and duration of deafness in left-ear implanted individuals. In general, open symbols (circles, squares) represent unilaterally implanted cochlear implant users, while filled symbols represent bilaterally implanted cochlear implant users, numbers alongside refer to patient number. Circles show activation in the auditory cortex, whereas squares indicate activation in the visual cortex.

Correlations between clinical parameters and activation in the visual and auditory cortex of cochlear implant users

Correlation analyses were performed separately for left and right ear implanted individuals because of substantial differences between the speech scores of the left and right ear in individuals with bilateral implants (Table 1). In light of the relatively small number of participants in each subgroup of cochlear implant users (six left-ear implanted, nine right-ear implanted individuals), Spearman's rank correlations were computed to explore the relation between clinical variables and activation in the visual and auditory cortex (Fig. 5). This analysis included the demographic factors 'duration of deafness' and 'duration of cochlear implant experience', as well as speech perception scores, assessed by two standard speech intelligibility tests, specifically the Freiburg monosyllabic word test (Hahlbrock, 1970; test for speech in quiet environment) and the Oldenburg sentences test (Wagener *et al.*, 1999; adaptive procedure that estimates the speech reception threshold, i.e. the signal-to-noise ratio for 50% word intelligibility). For right-ear implanted individuals, the analyses revealed negative correlations between speech intelligibility in the Freiburg monosyllabic word test and activation in the right auditory cortex (Level 3: $r = -0.78$, $P < 0.05$; Level 4: $r = -0.75$, $P < 0.05$). Similarly, the right-ear implanted individuals showed (near) significant positive correlations between the signal-to-noise ratio in the Oldenburg sentences test and activation in the auditory cortex of the right hemisphere (Level 3: $r = 0.63$, $P = 0.07$; Level 4: $r = 0.72$, $P < 0.05$). Moreover, duration of cochlear implant use and activation in the right visual cortex was negatively correlated in right-ear implanted cochlear implant users (Level 1: $r = -0.68$, $P < 0.05$). Finally, for left-ear implanted individuals, we found a positive correlation between duration of deafness and activation in the visual cortex of the right hemisphere (Level 4: $r = 0.93$, $P < 0.01$). Because of the relatively small number of samples in each subgroup of cochlear implant users, the generalization of our results may be limited. However, we estimated the reliability of the observed correlations by using a split-half reliability

approach (Walhovd and Fjell, 2002; McArthur *et al.*, 2003). In this procedure, the EEG data of each participant were split in even and odd trials. Afterwards, correlations between speech intelligibility and current source densities were separately computed for even and odd trials. The comparison of correlations for even and odd trials revealed a similar pattern of results (Supplementary Fig. 3). In particular, the Spearman's rank correlation coefficients indicate that correlations were similar for even and odd trials, indicating a low level of residual noise in the data. Taken together, this finding suggests that our correlation results are reliable.

Discussion

The present study examined cross-modal reorganization in the auditory cortex of post-lingually deafened cochlear implant users. This was carried out using EEG source imaging, which allowed the study of auditory cortex activity in response to visual stimulation. For the P100 VEP, the results revealed smaller amplitudes and reduced activation in the visual cortex in cochlear implant users compared with normal-hearing listeners. At the P100 latency, cochlear implant users also showed recruitment of the right auditory cortex to purely visual stimulation. This activation of the auditory cortex was inversely related to speech perception ability in right-ear implanted cochlear implant users. Our results confirm a visual take-over type of reorganization in the auditory cortex of cochlear implant users. Importantly, the degree of this cross-modal reorganization was systematically related to speech recognition ability with a cochlear implant.

Changes in visual-evoked potentials of cochlear implant users

The present study revealed a parametric modulation of P100 amplitudes as a function of luminance ratio in the chequerboard images. This result was found in both cochlear implant users and normal-hearing listeners and is consistent with previous findings of larger VEP responses for higher luminance levels in the visual stimuli (Armington, 1968; Johannes *et al.*, 1995). However, our results revealed smaller P100 amplitudes and reduced visual cortex activation in cochlear implant users compared with normal-hearing listeners. This suggests that cochlear implant users show functional changes in the central visual system as a consequence of altered auditory experience, in particular auditory deprivation and subsequent electrical reafferentation after implantation. Thus, auditory experience (or the lack thereof) may affect not only auditory (Henkin *et al.*, 2004; Sharma *et al.*, 2005; Pantev *et al.*, 2006; Sharma and Dorman, 2006; Gilley *et al.*, 2008; Sandmann *et al.*, 2009, 2010), but also visual functions in cochlear implant users (Doucet *et al.*, 2006; Buckley and Tobey, 2011). Indeed, functional changes in both the visual and auditory cortices have been observed over the first months and years after cochlear implantation (Giraud *et al.*, 2001*b*; Strelnikov *et al.*, 2010).

Changes in visual cortical areas have also been reported for deaf individuals, corroborating the view of functional changes in the central visual system as a consequence of long-term alteration of auditory experience (Bavelier *et al.*, 2006; Mitchell and Maslin, 2007). In contrast to our finding of reduced VEP amplitudes and smaller visual cortex activation in cochlear implant users, however, several studies on deaf individuals have reported enhanced VEP amplitudes (Neville and Lawson, 1987; Armstrong *et al.*, 2002) and larger recruitment of visual cortical areas in deaf individuals compared with normal-hearing listeners (Bavelier *et al.*, 2001; Fine *et al.*, 2005; but see Chlubnova *et al.*, 2005). This increase in cortical activation has been related to superior visual abilities in deaf individuals (Neville and Lawson, 1987). Accordingly, it can be predicted that our result of smaller P100 amplitudes and reduced visual cortex activation in cochlear implant users may reflect a visual deficit in these individuals. However, we are reluctant to draw firm conclusions on visual abilities in cochlear implant users based on our results, because we did not record any behavioural data in our experiment. Moreover, a direct transfer of results from deaf individuals to cochlear implant users should be taken with caution since cochlear implant users experience both auditory deprivation as well as sensory input after implantation, and these experiences might be associated with specific changes in the visual and auditory system (Rouger *et al.*, 2011). Nevertheless, previous results suggest that cochlear implant users develop strong visual speech-reading skills during the period of deafness, and these superior visual abilities are maintained or even improved after cochlear implantation, despite progressive recovery of auditory function (Tyler *et al.*, 1997; Rouger *et al.*, 2007, 2011; Strelnikov *et al.*, 2010; Giraud *et al.*, 2011*a*). This finding argues against a visual deficit in cochlear implant users, at least for the processing of natural speech stimuli.

The present results revealed shorter P100 latencies in cochlear implant users than in normal-hearing listeners specifically for the condition with the lowest luminance ratio. However, no between-group difference was found for the conditions with higher luminance ratios in the stimulus pattern (Levels 2–4). VEP latencies can provide estimates of visual processing time (Thorpe *et al.*, 1996) and might co-vary with latency in the behavioural response in visual tasks (Hartwell and Cowan, 1994; Fort *et al.*, 2005). This leads to the prediction that our finding of reduced P100 VEP latencies in cochlear implant users may reflect shorter, more efficient visual information processing that allows faster behavioural response in these individuals. To date, however, it is not well understood whether cochlear implant users show enhanced (behavioural) response speed in visual tasks compared with normal-hearing listeners, although faster response times to visual motion stimuli have been reported in deaf individuals (Neville and Lawson, 1987; Bottari *et al.*, 2010). This behavioural enhancement in deaf individuals, in particular under peripheral attention has been related to stronger cortical activation in the motion-selective area MT and larger N1 VEP amplitudes (Neville and Lawson, 1987; Bavelier *et al.*, 2006). To the best of our knowledge, however, no study has so far reported a link between faster behavioural response and shorter VEP latencies in deaf individuals and cochlear implant users. This issue needs to be systematically addressed in future EEG studies on deaf individuals and cochlear implant users.

Explanations for visual-evoked potential differences between cochlear implant users and normal-hearing listeners

The current finding of different VEP amplitudes between cochlear implant users and normal-hearing listeners could be due to at least two different neural mechanisms. First, smaller scalp-recorded VEP amplitudes in cochlear implant users might originate from higher variability of single-trial P100 latencies, which would manifest as lower P100 amplitude overall in cochlear implant users compared with normal-hearing listeners (Spencer, 2005). However, our VEP single-trial latency jitter analysis renders this interpretation unlikely.

An alternative explanation for smaller scalp-recorded P100 amplitudes in cochlear implant users than in normal-hearing listeners is the reduced recruitment of visual cortical areas in cochlear implant users. Consistent with this view, the P100 VEP source analysis revealed smaller activation in the visual cortex of cochlear implant users compared with normal-hearing listeners, indicating either smaller assembly or reduced synchronization of activated neurons in the visual cortex of cochlear implant users (Nunez, 1981). Unfortunately, the two mechanisms cannot be unravelled from EEG, but the observed group differences for short-latency P100 VEPs clearly suggest that auditory experience (or the lack thereof) can significantly alter early, initial stages of visual information processing that are strongly influenced by physical stimulus properties. This is in contrast to a previous study, which has shown a difference between normal-hearing listeners and cochlear implant users specifically for the later P2 VEP component (~230 ms post-stimulus onset) (Doucet *et al.*, 2006). The P2 VEP reflects a later, higher order processing stage than the P100 VEP and can therefore be assumed to be more under the influence of top-down cognitive mechanisms. Thus, the results of the two studies complement each other by suggesting that alteration of auditory experience affects visual processes both at early and later processing levels in the visual hierarchy.

Nevertheless, our result of smaller P100 amplitudes in cochlear implant users seems to be at odds with the previous observation of larger P2 amplitudes in cochlear implant users (Doucet *et al.*, 2006). This putative discrepancy of results is likely attributable to variations in methodology, in particular in terms of the types of the visual stimuli and the variability in the groups of participants. Doucet and colleagues (2006) successively presented two images with concentric and star-shaped grating to induce shape transformation and to compare VEPs between normal-hearing listeners and a heterogeneous group of cochlear implant users. In particular, the study examined cochlear implant users with poor and good speech recognition ability, using sign language and oral communication mode, respectively. This is in contrast to our study that used parametrically modulated chequerboard images to specifically compare exogenous effects on early VEPs in normal-hearing listeners and cochlear implant users with moderate to good speech recognition ability (mean and standard error: $83 \pm 3.3\%$; range: 60–100%). Thus, the substantial methodological differences between the two studies may at least partly account for the discrepancy of the results. Importantly, the opposite findings of the two studies for early and later processing levels in the visual hierarchy are not mutually exclusive, since the studies used different types of visual stimuli to test cortical functions at different levels of visual hierarchy.

Activation in the auditory cortex for visual processing

The results of the P100 VEP source analysis revealed that purely visual stimulation elicited larger activation in the auditory cortex of cochlear implant users than normal-hearing listeners. In contrast, the visual cortex was more strongly activated in normal-hearing listeners than in cochlear implant users for visual processing. This interaction between auditory and visual cortices suggests that activation in the auditory cortex of cochlear implant users cannot be explained by simple volume conduction across the tissues that separate cortex from scalp electrodes. Moreover, our finding supports previous results on deaf individuals, showing that visual stimulation activates the auditory cortex of deaf, but not hearing, individuals (Nishimura *et al.*, 1999; Petitto *et al.*, 2000; Finney *et al.*, 2001, 2003; Fine *et al.*, 2005). Similar to the current results, visually induced activation of the deaf auditory cortex has been observed predominantly in the right hemisphere, suggesting hemispheric differences for visual information processing (Finney *et al.*, 2003; Fine *et al.*, 2005). Whether this cross-modal activation of the deaf auditory cortex affects both the primary and higher level auditory areas remains open (Finney *et al.*, 2001; Kral *et al.*, 2003, 2007; Fine *et al.*, 2005), as a reliable distinction between primary and secondary auditory cortex seems challenging with the moderate spatial resolution of EEG source localization (Pascual-Marqui, 2002). Therefore, future neuroimaging studies on deaf individuals are needed to systematically unravel the capacity of different subregions of auditory cortex for cross-modal reorganization.

The evidence available supporting visual-induced activation of auditory cortex in cochlear implant users suggests a visual-to-auditory cross-modal type of reorganization as a consequence of sensory deprivation (Bavelier and Neville, 2002; Merabet and Pascual-Leone, 2010). Cross-modal reorganization of the deaf auditory cortex may provide the neural basis for specific superior visual abilities, such as the detection and discrimination of visual motion in the peripheral visual field (Bavelier *et al.*, 2006). Support for this assumption comes from a recent animal study, showing a causal link between improved visual abilities and visual activity in the reorganized auditory cortex of deaf cats (Lomber *et al.*, 2010).

How can the current finding of cross-modal recruitment of auditory cortex in cochlear implant users be explained? First, activation of the auditory cortex for visual processing in cochlear implant users may reflect increased cross-modal binding between the visual and auditory system in these individuals. Enhanced audio–visual coupling in cochlear implant users has been suggested by a previous brain imaging study, showing particular involvement of low-level visual cortical regions during listening to words (Giraud *et al.*, 2001*a*). Moreover, cochlear implant users have better abilities of visuo-auditory integration than normal-hearing listeners (Rouger *et al.*, 2007), suggesting that mutual reinforcement of visual and auditory modalities after implantation might represent

a specific compensatory strategy to overcome the degraded auditory signal provided by a cochlear implant. Thus, experience with a cochlear implant may enhance cross-modal interactions between visual and auditory cortical areas because of limitations in the implant signal. Indeed, cochlear implant users improve not only in speech but also in lip-reading comprehension during the first years following implantation (Tyler *et al.*, 1997; Giraud *et al.*, 2001*a*).

Alternatively, the current finding of visual-induced activation of auditory regions in cochlear implant users might reflect residual compensatory reorganization of the auditory cortex. Cross-modal reorganization induced by auditory deprivation may not completely vanish after implantation and restored sensory input probably because the capabilities of cortical reorganization are limited (Bavelier *et al.*, 2010). Accordingly, maladaptive cross-modal reorganization may preserve specifically in cochlear implant users with poor speech recognition abilities (Doucet *et al.*, 2006; Buckley and Tobey, 2011). Our results extend previous findings in that they show directly the recruitment of auditory cortex during visual information processing. In particular, our results revealed a negative relationship between visually induced activation of the auditory cortex and speech recognition ability with a cochlear implant. This relationship was found particularly for the right auditory cortex, which has been previously shown to be substantially involved in speech processing (Boemio *et al.*, 2005; Hickok and Poeppel, 2007). All in all, our results strongly suggest that residual cross-modal reorganization reflects a maladaptive process, which hinders the adaptation of auditory cortex neurons to the cochlear implant input. This interpretation is supported by the observation that pre-lingually deafened individuals with more pronounced cross-modal reorganization before implantation are less likely to benefit from a cochlear implant after implantation (Lee *et al.*, 2001, 2007; Giraud and Lee, 2007).

Mechanisms of cross-modal reorganization

Different mechanisms may mediate cross-modal reorganization of the deaf auditory cortex (Merabet and Pascual-Leone, 2010). One could be through the reinforcement of pre-existing connections between the auditory cortex and the intact sensory areas. Animal studies have shown that interactions between low-level sensory cortical regions might be subserved by direct heteromodal connections (Falchier *et al.*, 2002; Rockland and Ojima, 2003; Cappe and Barone, 2005; Hall and Lomber, 2008). In agreement with this anatomical finding are results from intracranial recordings, suggesting direct visual and somatosensory input in regions posterior to A1 (Schroeder and Foxe, 2005). Additional evidence for direct cross-modal interactions between the visual and auditory system comes from a recent human study, showing visual-induced modulation of activity in auditory cortex (Thorne *et al.*, 2011).

A second mechanism underlying cross-modal plasticity could be through the alteration of corticocortical feedback connections from multisensory brain regions. Consistent with this view, deaf individuals show functional changes in the multisensory parietal cortex (Bavelier *et al.*, 2001) and enhancements in feedback connectivity from parietal cortex to lower level visual cortical areas (Bavelier *et al.*, 2000). Overall, these two mechanisms are not mutually exclusive and may jointly mediate the recruitment of the auditory cortex by the remaining modalities.

Conclusion

The present study compared VEP source activity in cochlear implant users and normal-hearing listeners to examine cross-modal reorganization in the auditory cortex of cochlear implant users. Implant users showed activation in the right auditory cortex for visual processing, which was negatively related to speech recognition ability with a cochlear implant. Despite the relatively small sample size investigated, this finding suggests cross-modal reorganization in the auditory cortex of cochlear implant users as a result of long-term alteration of auditory experience. Importantly, the cross-modal recruitment of auditory cortex was found at initial stages of visual information processing. Incomplete reversal of this deafness-induced reorganization may limit auditory benefit from a cochlear implant and might help explain the high variability in performance outcomes observed in cochlear implant users.

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Supplementary material

Supplementary material is available at *Brain* online.

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